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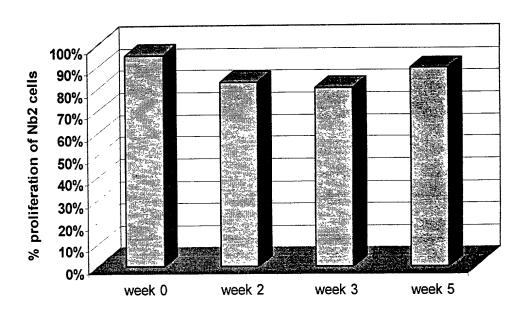


Figure 1

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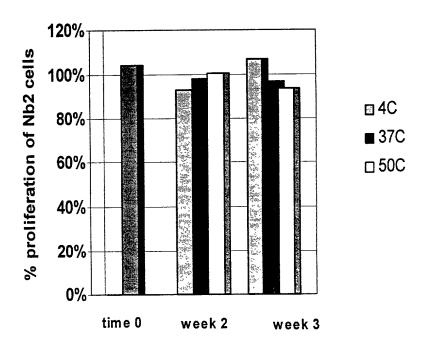


Figure 2

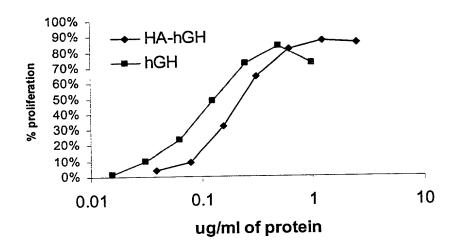


Figure 3A

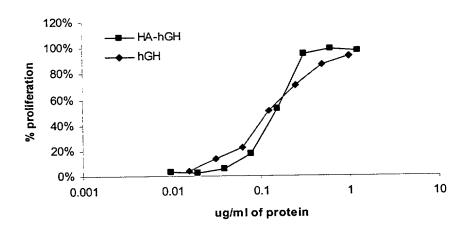


Figure 3B

Man den day hay had

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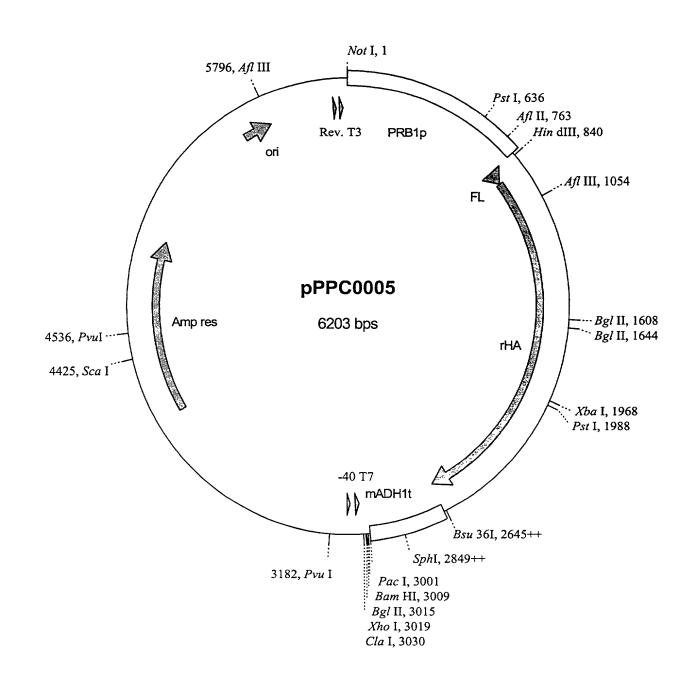


Figure 4



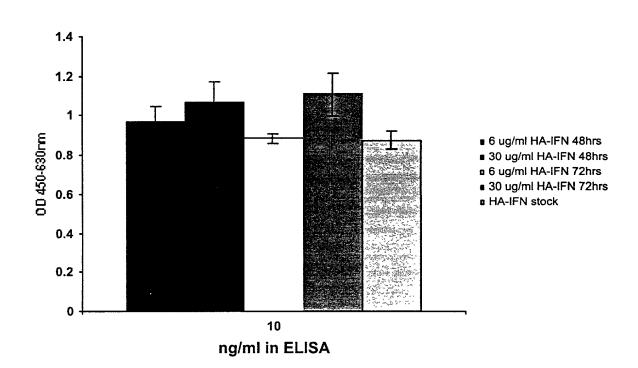
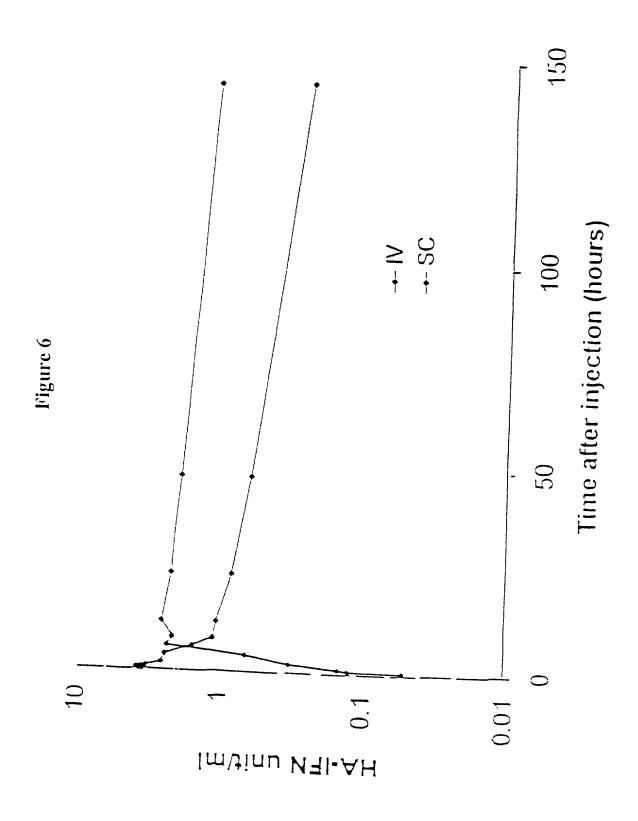


Figure 5



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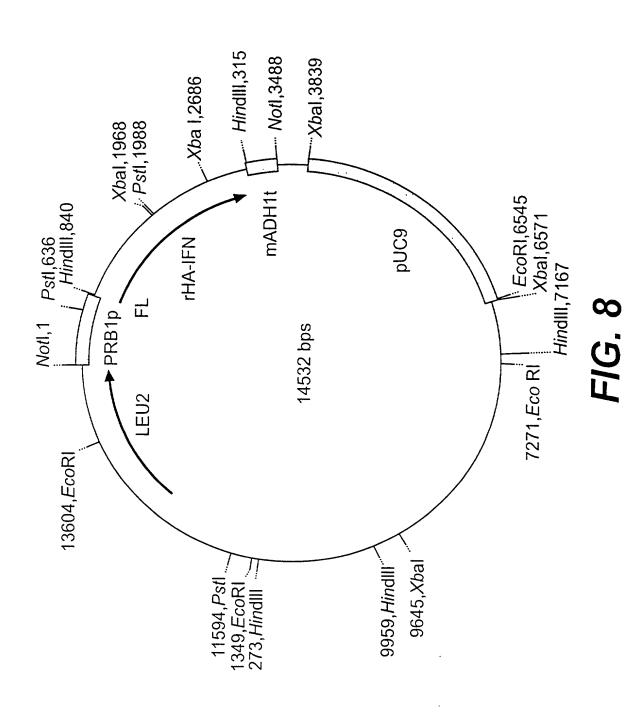


Figure 9

1			ALVLIAFAQY ННННННННН	LQQCPFEDHV HHHHH		
51	I KTCV ADESAE HHHHH	N CDKSLHTLF HHHHH	GDKLC TVATL HHHHH	II RETYGEMA DC HHHH		
101	CFLQHKDDNP HHHH			EETFLKKYLY HHHHHHHHH		
151		ҮКААГТЕСС о ННННННННН	IV AADKAACLLP HHHHH	KLDELRDEGK НННЕННННН	ASSAKQRLKC ННННННННН	
201	ASLQKFGERA HHHHH HH	FKAWAVARLS ННННННННН	QRFPKAEFAE HH HHH	VSKLVTDLTK ННННННННН	V VHTECC HGDL HHHHHHH HH	
		v	'I	VII		
251	LE CADDRADL ННННННННН	AKYIC ENODS	_	KPLLEKSHCI HHHHHHH		
301	DLPSLAADFV HHHH	ESKDVCKNYA HHHHHH		LYEYARRHPD HHHHHH	YSVVLLLRLA HHHHHHHH	
351	КТҮЕТТLЕКС ННННННННН	VIII C AAADPHE CY HH		VEEPQNLIKQ ННННННННН		
401	YKFQNALLVR ННННННННН			GKVGSKCC <u>KH</u> HHH	IX PEAKRMP CAE HHHHHHHH	
451	DYLSVVLNQL ННННННННН	X CVLHEKTPVS HHHHH	DRVTKCCTES HHHHHHHHH	XI LVNRRPPCFSA HHHHHHHH	LEVDETYVPK	
501	EFNAETFTFH		RQIKKQTALV ННННММЕННН	ELVKHKPKAT HHH	KEQLKAVMDD ННННННН	
551	FAAFVEKCC K НННННННН		EGKKLVAASQ ННННННННН			
	II Thr7 III Ala9 IV Gln1 V His2	4-Asn61 6-Asp89 2-Glu100 70-Ala176 47-Glu252 66-Glu277	Loop VII VIII IX X XI XII	Glu280-His288 Ala362-Glu368 Lys439-Pro447 Val462-Lys475 Thr478-Pro486 Lys560-Thr566		

Figure 10

a. Randomisation of Loop IV.

IV

IV

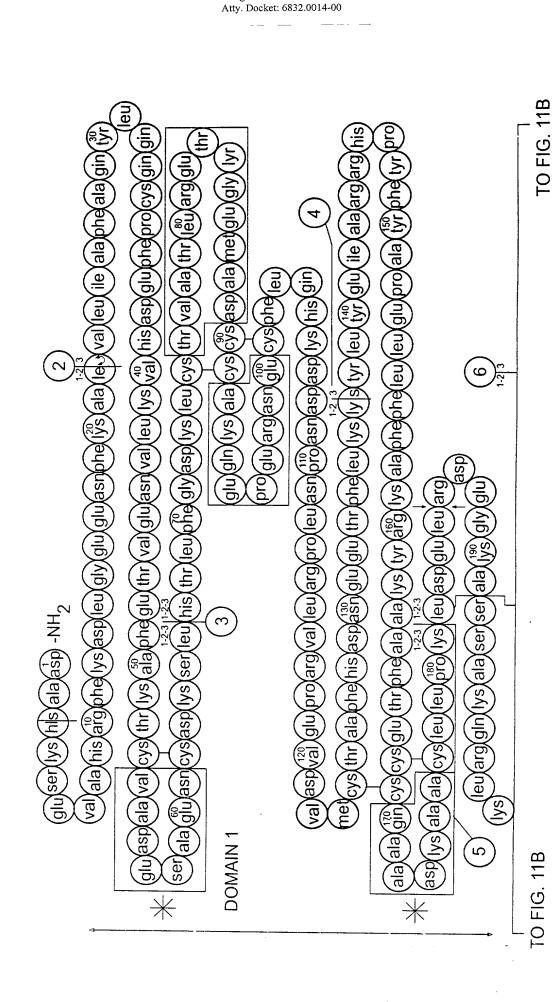
X represents the mutation of the natural amino acid to any other amino acid. One, more or all of the amino acids can be changed in this manner. This figure indicates all the residues have been changed.

b. Insertion (or replacement) of Randomised sequence into Loop IV.



IV

The insertion can be at any point on the loop and a length where n would typically be 6, 8, 12, 20 or 25.



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FIG. 11A

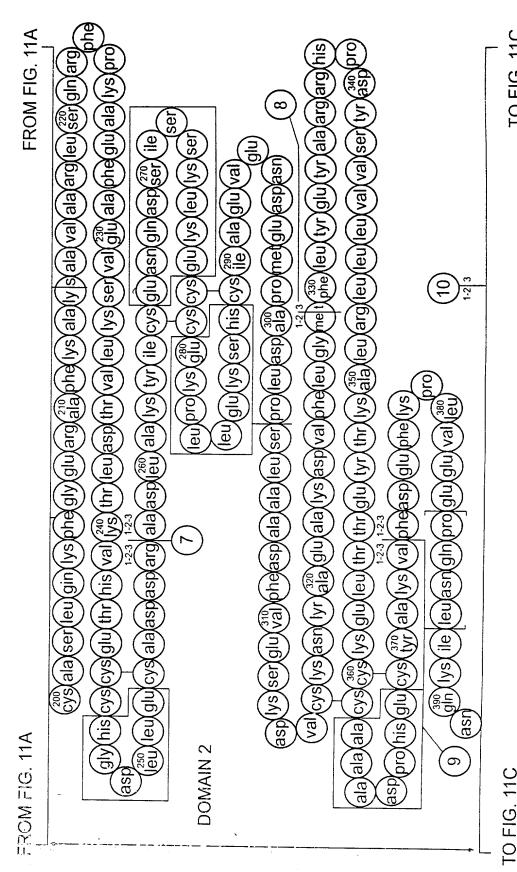


FIG. 11B

TO FIG. 11C

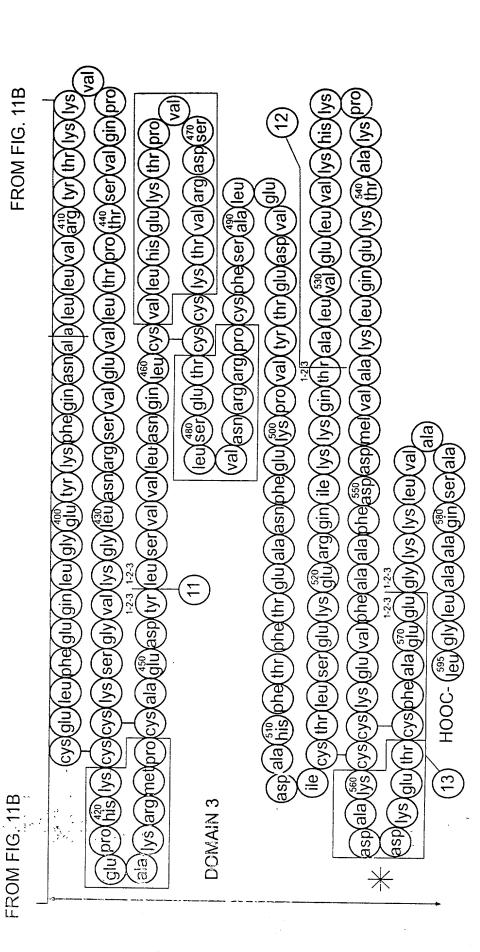


FIG. 11C

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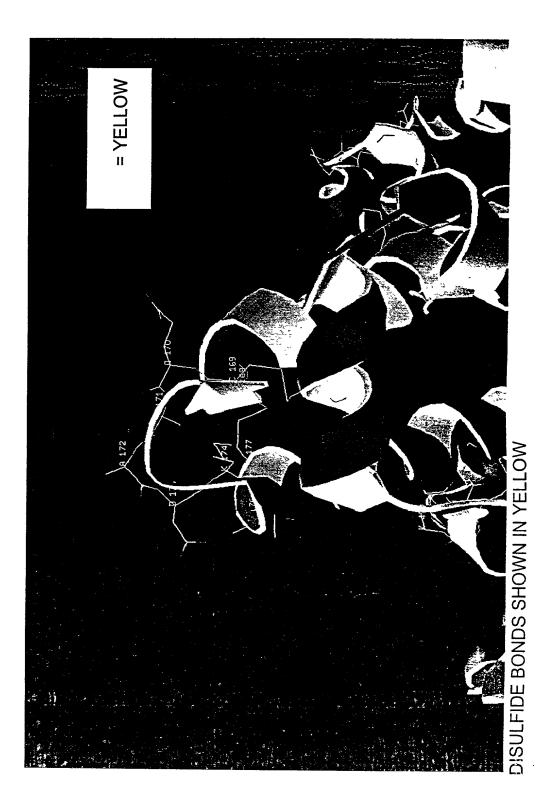


FIG. 12: LOOP IV GLU170-A176

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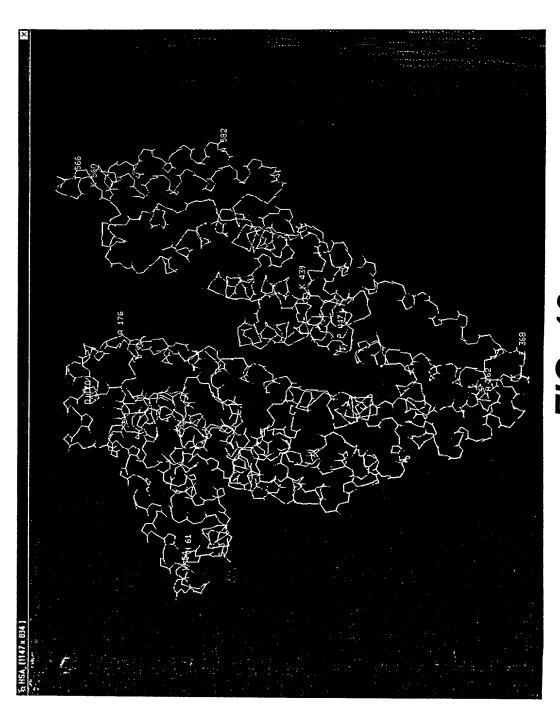
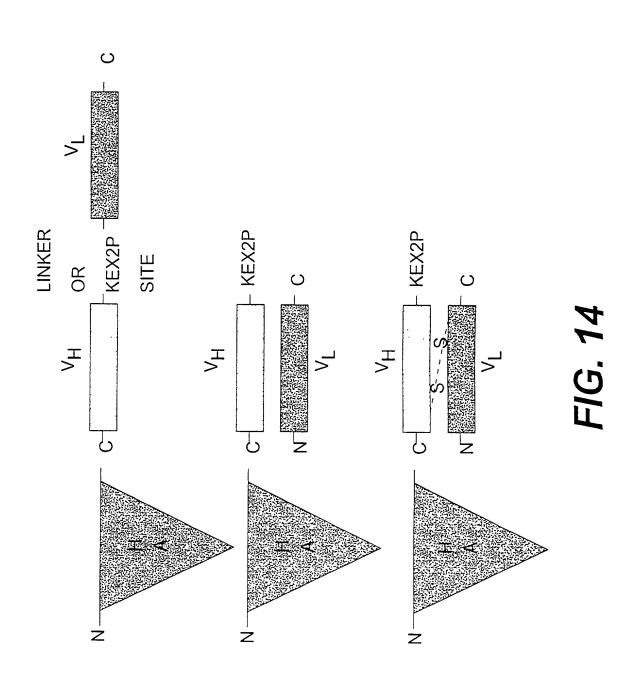


FIG. 13 TERTIARY STRUCTURE OF HA



60

120 40 180 60 240 80 300 100 360 120 420 140 AAT GAG E AGA GAA ACA CCT P GTG AAA CCATGC C GGA GAA E TTGД TTG CGA $_{ m TGT}$ CAA GAT $_{\rm C}$ AAA K AAA K AAA ACA GAG E CAG GCA A GAC D CICCCG P TIT AAA K TGT C GAA E GGA G AAC N SSS GCA A $_{ m F}$ TAT Y TAT TGC C CCAAAT N Д CATTTT F CAG CTTGAC D AAC N GAC $_{ m TTT}$ Ø GAA ATG GCT (E M A I GAA E GCTACC T GAC CAT TAC GCT Ω CAT H GAG GTT ACT GAT GTA AAA AGT $_{ m GGT}$ CAC TCA S . AAG 7. K · TTG . AAT N AAA K $_{ m TAT}$ CAA CAC GTG V ACC T GAC D TTGATG M 229 GCA GAA E TTC $_{\rm C}^{ m TGT}$ GATCCC AAA K AAT N CGT R TGC \circ 121 181 61 241 81 61 21

540 180	600	660	720	780 260	840 280	900	960 320
CCA	TGT C	CGC CTG AGC (CTT ACC AAA 3	CTT	GAA E	GCT A	GCT A
${ m TTG}$	AAA K	CTG L	ACC	AGG GCG GAC OR A DOC	AAA CIG AAG GAA TGC TGT K L K E C C	CCT	TAT Y
$_{ m L}^{ m CTG}$	CTC	CGC R	$_{\rm L}^{\rm CTT}$	GCG A	TGC	ATG M	AAA AAC K N
TGC C	AGA R	GCT A	GAT D	AGG R	GAA E	GAG	AAA K
GCC	CAG Q	GTG V	ACA T	GAC D	AAG K	GAT D	TGC
GCT A	AAA CAG K Q	GCA GTG A	GTG V	GAT D	CTG L	AAT N	GTT V
AAA K	GCC	TGG W	S TTA GTG ACA GAT C L V T D L	GCT GAT GAC A A D D I	AAA K	GAA AAT E N	GAT D
GAT D	TCG TCT S S	GGA GAA AGA GCT TTC AAA GCA G E R A F K A	A AA(GGA GAT CTG CTT GAA TGT G D L L E C	CAG GAT TCG ATC TCC AGT Q D S I S S	TG	A.A.G K
GCT A	TCG	AAA K	TCC	GAA E	TCC	GAA E	AGT S
GCT A	GCT A	TTC	GTT V	$_{\rm L}^{\rm CTT}$	ATC I	GCC A	GAA E
CAA Q	GAT GAA GGG AAG GCT DE GKAA	GCT A	G TTT GCA GAA GTT TV F A E V S	cTG L	TCG	C CAC TGC ATT GCC GAA G' H C I A E V	GTT GAA AGT . V E S
IGC C	999	AGA R	GCA A	GAT D	GAT D	TGC	TTT F
TGT C	GAA E	GAA E	${ m TTT}$	GGA G	CAG Q	CAC H	GAT D
GAA E	GAT D	GGA G	E GA.	CAT H	AAT N	TCC S	GCT A
ACA T	CGG R	, AAA TTT (K F (AAA GCT K A	TGC	TGT GAA Z	AAA K	GCT A
TTT	GAA CTT E	AAA K	AAA K	TGC	TGT	GAA	${f TTA}$
GCT A	GAA E	CAA Q	CCC	GAA E	ATC I	TTG L	TCA S
GCT A	GAT D	CTC L	TTT F	ACG T	TAT	${ m CTG}$	CCT P
AAA K	CTC	AGT S	AGA R	CAC H	AAG K	CCT P	TTG L
TAT Y	AAG K	GCC	CAG Q	GTC V	GCC	AAA K	GAC D
481 161	541	601	661	721 241	781 261	841	901 301

Figure 15B

1020 340	1080 360	1140 380	1200	1260 420	1320 440	1380 460	1440 480
GAG GCA AAG GAT GTC TTC CTG GGC ATG TTT TTG TAT GAA TAT GCA AGA AGG CAT CCT GAT E A K D V F L G M F L Y E Y A R R H P D	TGC C	TGT GCC GCT GCA GAT CCT CAT GAA TGC TAT GCC AAA GTG TTC GAT GAA TTT AAA CCT CTT	GAG E	ACT T	CAT H	TTA L	TCC S
CCT P	AAG K	CCT	GGA G	TCA S	AAA K	CAG Q	GAG E
CAT H	GAG	AAA K	$_{\rm L}^{\rm CTT}$	GTG V	TGT C	AAC N	ACA T
AGG R	CTA L	TTT E	CAG Q	CAA Q	TGT C	CTG L	TGC
AGA R	ACT	GAA E	GAG E	CCC	AAA K	GTC V	TGC
GCA A	ACC T	GAT D	TTT E	GTA V	AGC S	GTG V	AAA K
TAT Y	GAA E	TTC F	CTT L	AAA K	667 6	TCC	ACA T
GAA E	TAT Y	GTG V	GAG E	AAG K	GTG V	$_{\rm L}^{\rm CTA}$	GTC V
TAT Y	ACA T	AAA K	TGT	ACC T	AAA K	TAT Y	AGA R
$_{ m L}^{ m TTG}$	AAG K	GCC A	AAC N	TAC Y	GGA	GAC D	GAC D
TTT F	GCC A	TAT Y	CAA Q	CGT R	CTA L	GAA E	AGT S
ATG M	$_{\rm L}^{\rm CTT}$	TGC	AAA K	GTT V	AAC N	GCA A	GTA V
GGC	AGA R	GAA E	ATC I	TTA L	AGA R	TGT C	CCA P
CTG L	cTG	CAT H	TTA L	CTA L	TCA S	CCC P	ACG T
TTC F	$_{ m L}^{ m CTG}$	CCT	AAT N	GCG A	GTC V	ATG M	AAA K
GTC V	$_{\rm L}^{\rm CTG}$	GAT D	CAG Q	AAT N	GAG E	AGA R	GAG E
GAT D	GTG V	GCA A	CCT P	CAG Q	GTA V	AAA K	CAT H
AAG K	GTC V	GCT A	GAG E	${\rm TTC}_{\rm F}$	CTT L	GCA A	$_{ m L}^{ m TTG}$
GCA A	TCT	GCC A	GAA E	AAA K	ACT T	GAA E	GTG V
GAG E	TAC Y	TGT	GTG V	TAC Y	CCA P	CCT P	TGT
961 321	1021 TAC TCT GTG CTG CTG AGA CTT GCC AAG ACA TAT GAA ACC ACT CTA GAG AAG TGC 341 Y S V V L L L R L A K T Y E T T L E K C	1081	1141 GTG GAA GAG CCT CAG AAT TTA ATC AAA CAA AAC TGT GAG CTT TTT GAG CAG CTT GGA GAG 381 V E E P Q N L I K Q N C E L F E Q L G E	1201 TAC AAA TTC CAG AAT GCG CTA TTA GTT CGT TAC ACC AAG AAA GTA CCC CAA GTG TCA ACT 1260 401 Y K F Q N A L L V R Y T K K V P Q V S T 420	1261 CCA ACT CTT GTA GAG GTC TCA AGA AAC CTA GGA AAA GTG GGC AGC AAA TGT TGT AAA CAT 1320 421 P T L V E V S R N L G K V G S K C C K H 440	1321 CCT GAA GCA AAA AGA ATG CCC TGT GCA GAA GAC TAT CTA TCC GTG GTC CTG AAC CAG TTA 1380 441 P E A K R M P C A E D Y L S V V L N Q L 460	1381 TGT GTG TTG CAT GAG AAA ACG CCA GTA AGT GAC AGA GTC ACA AAA TGC TGC ACA GAG TCC 1440 461 C V L H E' K T P V S D R V T K C C T E S 480

Figure 15C

GAA GTC GAT GAA ACA TAC GTT CCC AAA 1500 E V D E T Y V P K 500 1560 AAG GCA ACA 1620 K A T 540 TGC TGC AAG 1680 C C K 560 GCT GCA AGT CAA 1740 A A S Q 580 520 TCT GAG AAG GAG AAG K GTG AAA CAC AAG CCC V K H K P CTT ' GTA GAG A AAG GAG ACC TGC TTT GCC GAG GAG GGT AAA AAA CTT GTT K E T C F A E E G K K L V TTA TAA CAT CTA CAT TTA AAA GCA TCT CAG 1782 GCA GAT ATA TGC ACA TTTGCT A GAG CTT (E L GCA GCT CTG TTC A ACC TTC CAT T F H GTL GAG CAA CTG AAA GCT GTT ATG GAT GAT E Q L K A V M D D Ø TCA CII TTT GCA Ŀ TTC TGC AAG AAA CAA ACT K K Q T 1441 TTG GTG AAC AGG CGA CCA 481 L V N R R P GCT GAA ACA TTA GGC CAA ATC A Q I F AAT GAT Z Ω ${ m TTT}$ GAC 1741 GCT GCC 581 A A 1621 AAA (541 K 1561 AGA (GAG E 1681 GCT 561 A 1501 501

Figure 15D